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Prevention of sudden cardiac arrest in dialysis patients: can we do more to improve outcomes?

Bessie A. Young[1,2]

Sudden cardiac arrest (SCA) is a leading cause of cardiac-associated mortality in dialysis patients. Risk factors unique to hemodialysis patients include abnormal electrolytes, large-volume ultrafiltration, and prior history of cardiac disease. Few randomized controlled trials of standard cardiac interventions have been completed in dialysis patients. Observational studies suggest that modification of the dialysis prescription may be one place to intervene. Prospective research is needed to determine mechanisms of SCA in hemodialysis patients.

Kidney International (2011) **79,** 147–149. doi:10.1038/ki.2010.433

Cardiac disease remains the primary cause of death among dialysis patients (84.5 per 1000 patient-years) and accounts for 39.2% of all deaths.[1] Mortality associated with sudden cardiac death or sudden cardiac arrest (SCA) accounts for 58.6% of cardiac-related deaths (49.5 per 1000 patient-years).[1] As expected, SCA-associated death is higher among the elderly and those with a cardiac history and among whites compared with blacks and other minorities.[1] In addition, SCA is known to occur more often on the first dialysis day after a 2-day hiatus,[2,3] with the risk being highest during and immediately after dialysis.[4] SCA is five- to 15-fold more likely to result from either ventricular fibrillation or ventricular tachycardia during or immediately after dialysis, whereas a pulseless electrical activity arrest is more likely to occur before dialysis.[3] Rates of sudden death per dialysis session range from 3.4 in 100,000[3] to 7.0 in 100,000[5] dialysis sessions in the outpatient setting and to 12.5 in 100,000 dialysis sessions in hospital-based dialysis units.[5]

Risk factors associated with SCA include older age,[6] history of underlying diabetes,[6,7] increased inflammation,[8] recent hospitalization,[6] low-potassium dialysate,[6] malnutrition,[6] use of a catheter for dialysis access,[6] left ventricular hypertrophy,[9] increased levels of brain natriuretic peptide or N-terminal-pro-B-type natriuretic peptide (nT-pro-BNP),[10] rapid changes in electrolytes or large-volume fluid removal, and prior history of cardiac disease or arrhythmia.[4,6] In a landmark paper, Karnik and colleagues reported that a low-potassium bath of 0 or 1 mequiv. per liter was associated with a greater risk of cardiac arrest (17.1% versus 8.8%); however, low-K^+ dialysate baths did not account for all cases of cardiac arrest.[6] Additional proposed SCA triggers include reduced left ventricular function, ventricular ectopy, interstitial fibrosis due to chronic uremia, calcium and phosphate deposition, chronic fluid overload, and generalized electrical instability due to fluid shifts, acid/base abnormalities, and other electrolyte abnormalities.[11–13] Myocardial stunning, which is thought to occur with each dialysis session and is due to excessive volume and electrolyte shifts, may also contribute to the increased risk of SCA in dialysis patients.[13,14]

Few randomized controlled trials have evaluated interventions aimed at reducing SCA in dialysis patients. Observational data suggest that use of beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers has been associated with decreased overall mortality.[15] In addition, automatic defibrillator placement in dialysis units has not been shown to be associated with improved survival of hemodialysis patients after SCA.[3,16] No randomized controlled trial of implantable cardiac defibrillators (ICDs) in dialysis patients has ever been completed; however, observational studies have shown that ICD placement was associated with a 42% reduction in mortality in comparison with those without ICD placement.[17] Implantable defibrillators are sorely underutilized in dialysis patients,[17,18] and the Implantable Cardioverter Defibrillators in Dialysis Patients (ICD2) trial is a current randomized controlled trial enrolling approximately 200 dialysis patients aged 50–80 years with prevention of SCA as the primary end point.[19]

Now, Pun and colleagues[20] (this issue) describe a case-control study that evaluated potentially modifiable risk factors for SCA among a large cohort of dialysis patients from 2002 to 2005. Among 43,200 DaVita/Gambro dialysis patients, 784 witnessed SCAs were documented for an

[1]*Epidemiologic Research and Information Center, Seattle VA Puget Sound Healthcare System, Seattle, Washington, USA and* [2]*Kidney Research Institute, Division of Nephrology, University of Washington, Seattle, Washington, USA*
Correspondence: *Bessie A. Young, Seattle Epidemiologic Research and Information Center, VA Puget Sound Health Care System, 1660 S. Columbian Way, 152-E, Seattle, Washington 98108, USA. E-mail: youngb@u.washington.edu*

Table 1 | Modifiable risk factors for prevention of sudden cardiac arrest in hemodialysis patients

Risk factor	Possible solution
Low predialysis serum potassium	Use dialysate algorithm to automatically adjust dialysate potassium bath
Low dialysate potassium concentration	Remove 0- and 1-mequiv.-per-liter-potassium dialysate baths from dialysis units
Low dialysate calcium concentration	Remove low-calcium dialysate baths below 2.0 mequiv. per liter
High serum potassium	Adjust dialysate potassium and check potassium during the run
Rapid fluid shifts during dialysis	Limit upper-range amount of fluid removal per hour or per run; consider short daily or nocturnal dialysis[22]
Hospitalization/acute events	Reevaluate serum electrolytes, dialysate potassium/calcium, and volume status after acute events[22]
Cardioprotective medications	Randomized controlled trial data needed
Automatic defibrillators, implantable defibrillators	More data needed

Reference: Ostermann.[22]

event rate of 4.5 per 100,000 dialysis sessions, or 1 in 142 patient-years. After exclusions, 502 SCA patients were matched to 1632 age- and dialysis vintage-matched controls. The authors found that dialysate potassium prescriptions less than 2.0 mequiv. per liter were associated with a 2.06-fold (confidence interval 1.48–2.86) greater probability of SCA, and low dialysate calcium prescriptions less than 2.5 mequiv. per liter were associated with a 1.88-fold (confidence interval 1.28–2.76) greater probability of SCA events, in comparison with matched controls in adjusted analysis. Greater ultrafiltrate volume removed during the dialysis session and a history of use of anti-arrhythmic drugs were also associated with greater odds of SCA, while serum calcium, phosphate, and parathyroid levels and history of cardiovascular disease were not. The authors confirmed that malnutrition (as determined by low serum albumin), lower serum creatinine, and lower levels of hemoglobin were also independently associated with an increased risk of an SCA event.

The authors also evaluated predialysis serum potassium levels and odds of SCA and found that many of the patients on lower-potassium baths also had low serum potassium levels at the most proximally recorded laboratory test. SCA risk was also shown to have a U-shaped distribution compared with the level of serum potassium; for example, potassium levels lower and higher than 5.1 mequiv. per liter were associated with greater probability of SCA. In this regard, the authors found that an interaction or effect modification existed between serum potassium and dialysate potassium level for low serum and dialysate potassium, which differed for those with higher levels of serum potassium, particularly serum levels above 6.0 mequiv. per liter. The authors state that they did not find any benefit of prescribing a dialysis potassium level less than 2.0 mequiv. per liter; however, they did not prove that there was harm in low dialysate potassium at a higher level of serum potassium greater than 6.0 mequiv. per liter.

The results of Pun *et al.*[20] are noteworthy and may have significant repercussions for dialysis-unit policy. Dialysis units and nephrologists should be more cognizant of low-predialysis-potassium baths and should consider adjusting dialysis potassium baths accordingly. After Karnik and colleagues published their seminal paper,[6] many dialysis units eliminated 0-mequiv.-per-liter-potassium dialysate baths because of concern about increased risk of SCA. Pun *et al.*[20] go a step further and raise the issue of whether patients should be dialyzing on any potassium bath less than 2.0 mequiv. per liter. This would have significant ramifications for home-based therapies, where $1K^+$ baths are the norm, and possibly for nocturnal dialysis as well, as low potassium exposure would be longer and the risk of SCA potentially greater in dialyzing against a low-potassium dialysate. Hopefully, data from the Frequent Hemodialysis Network randomized trial will help to clarify these concerns.[21]

Additional limitations of the paper by Pun *et al.*[20] should be noted. As the authors state, no labs were drawn the day of the SCA event, and hospitalizations proximal to the event are not known; thus, it is difficult to know whether there may be additional reasons for a low-potassium bath or increased risk of SCA. In addition, there is no information on difference in length of time of dialysis exposure between case and control. This information might help determine whether the length of time of exposure to low-K^+ dialysate is an additional inciting factor for SCA. The authors found negative associations with some common medications, such as anti-arrhythmic medication, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, which they correctly state are probably due to bias by indication. Additionally, the authors did not evaluate potential interactions between low calcium and dialysate potassium, which are two potential risk factors for SCA that may have a synergistic negative effect on cardiac membrane excitability. Finally, case-control studies are observational studies that best approximate randomized controlled trials; however, causality should still be cautiously interpreted.

In conclusion, Pun *et al.*[20] present an interesting and important paper on potentially modifiable risk factors for SCA that may have significant ramifications for hemodialysis patients in the United States and worldwide. Survival of cardiac arrest remains abysmal for dialysis patients, and only 15% of patients who have a cardiac arrest survive a year in the best of circumstances.[3] Prevention of this catastrophic outcome should be sought, and measures aimed to reduce modifiable risk factors should be undertaken (Table 1). Ultimately, nephrologists have control over the dialysis prescription and should be aware of low as well as high levels. Perhaps dialysis

centers need to have more actionable algorithms to monitor and decrease exposure to low dialysate potassium and calcium levels, and more diligence is needed on the part of clinicians regarding monitoring and adjustment of the dialysate prescription. Finally, more in-depth and mechanistic research is needed to evaluate potential SCA etiologies whereby effective interventions can be developed to prevent SCA in hemodialysis patients. Mortality rates remain unconscionably high for dialysis patients, and we, the nephrology community, must do all that is possible to prevent this deadly outcome.

DISCLOSURE
The author declared no competing interests.

ACKNOWLEDGMENTS
This work was supported by grant R01 DK079745 from the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, to Bessie Ann Young. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institute of Diabetes and Digestive and Kidney Diseases or the National Institutes of Health. This material is the result of work supported by resources from the VA Puget Sound Healthcare System, Seattle, Washington, USA.

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Am I my brother's keeper?: fratricide in the kidney

Robert L. Safirstein[1]

Experimental acute kidney injury (AKI) is accompanied by the death of renal tubule epithelial cells, necrosis and apoptosis of the terminal portion of the proximal tubule, and apoptosis in the distal nephron. While immune competent cells invading the kidney play a role in such cell death, intervention in these processes only partially ameliorates the extent of cell death. Given the results of Linkermann *et al.* in this issue of *KI*, an epithelium-derived component of immune mediated cell death must now be strongly considered.

Kidney International (2011) **79,** 149–150. doi:10.1038/ki.2010.441

Experimental acute kidney injury (AKI) is accompanied by the death of renal tubule epithelial cells, and the degree of renal dysfunction correlates with the extent of injury. In ischemic and cisplatin-induced AKI, cells of the terminal portion of the proximal tubule, which are most prominently involved, undergo necrosis while scattered cells throughout the nephron undergo apoptosis. How these cells die is the topic of active research, but recent focus has placed a major emphasis on the cells that mediate innate and adoptive immunity in the

[1]*Central Arkansas Veterans Healthcare System, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA*
Correspondence: *Robert L. Safirstein, Central Arkansas Veterans Healthcare System, University of Arkansas for Medical Sciences, 4300 West 7th Street (111/LR), Little Rock, Arkansas 72205, USA. E-mail: SafirsteinRobertL@uams.edu*